Common Variable Immunodeficiency in Adult Woman With IDDM

Common variable immunodeficiency (CVI) is a heterogeneous group of disorders characterized by hypogammaglobulinemia, as well as an abnormal immune regulation. Although patients with CVI frequently develop autoimmune diseases, the association of CVI with IDDM is an unusual event. Recent reports have suggested a genetic susceptibility for both clinical entities (1). Here we report a new patient with IDDM and CVI and comment on the obtained results of her HLA phenotype study.

The patient was 45 years old when she was admitted to the hospital because of fever, asthenia, hyperglycemia, and expectoration. There was no family history of chronic infections or autoimmune endocrinopathies. She had a history of tuberculosis in childhood. At the age of 21, IDDM was diagnosed. At 28 years of age, she began having recurrent upper and lower respiratory tract infections, persistent sinusitis, and diarrhea with steatorrhea associated with *Giardia lamblia* infection. At that time, the analysis of serum concentrations of immunoglobulins (Ig's) showed low levels of IgA. In the following years, she had multiple hospital admissions because of frequent metabolic decompensations secondary to respiratory infections and malabsorption syndrome. The patient had initiated tuberculostatic therapy after a sputum culture positive for *Mycobacterium tuberculosis* 5 days before entry. Initial laboratory evaluation showed hemoglobin 11.5 g/dl, hematocrit 35.6%, white cell count 8,150/mm^3, and glucose 281 mg/dl. The value of C-peptide was <0.1 ng/ml (N: 0.7–4.0). Immunological evaluation showed panhypogammaglobulinemia (IgG 213 mg/dl, N: 694–1,618; IgA 40 mg/dl, N: 68–378, and IgM 31 mg/dl, N: 60–263). Islet cell antibodies, insulin autoantibodies, and autoantibodies to GAD were negative. Total peripheral blood lymphocytes (1,710/mm^3), CD4 (43.7%) and CD8 (37.1%) T-cells, and CD4-to-CD8 ratio (1.18) were normal. The patient's HLA typing revealed A1, A30, B14, B18, BW4, CW5, DR3, and DR52 antigens. The patient was diagnosed with CVI and was started on intravenous immunoglobulin replacement therapy. In the following 12 months, the patient increased her body weight, and the frequency of infections decreased, improving the metabolic control of her diabetes.

We report a new case of hypogammaglobulinemia in an IDDM adult woman identified when she presented with recurrent respiratory infections and a malabsorption syndrome that affected her metabolic control. CVI is an incompletely defined syndrome characterized by defective antibody formation, and its diagnosis is based on exclusion of other known causes of humoral immune defects (2). This syndrome predisposes the patient to recurrent bacterial infections of the respiratory tract, gastrointestinal disorders, and autoimmune disorders. Of patients with CVI, ~20% develop one or more autoimmune diseases. The most common clinical forms affect the hematologic system, especially Coombs-positive hemolytic anemia and idiopathic thrombocytopenic purpura. Other less common autoimmune diseases are pernicious anemia, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome (3). Furthermore, IDDM patients are also prone to developing other autoinmmune disorders, such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, and pernicious anemia. To date, however, few reports have described the association of CVI and IDDM (1,4–7), and it has been proposed that a genetic predisposition to the development of these two diseases is linked to the major histocompatibility complex. Although a recent study has shown an increased relative risk of IDDM and/or CVI in subjects with HLA-B8, HLA-B14, and HLA-A29 (1), in the present case, we found such risk only with HLA-B14. On the other hand, another possible relationship with the HLA system is that our patient expressed HLA-A30, whereas the patient described by Metin et al. (1) showed HLA-A29, both being serologically HLA-A19. This would increase the genetic similarity described. Finally, HLA phenotype of our patient included HLA-A1 and HLA-DR3. These antigens were also found in the patient with CVI and IDDM described by Moffitt (6) in 1989. These findings support a genetic predisposition linked to the HLA system in the pathogenesis of these two disorders.

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References

1. Metin A, Tezcan I, Ozyurek H: IDDM in an adolescent patient with common variable immunodeficiency. *Diabetes Care* 20:677–678, 1997
2. Report of a WHO Scientific Group: Primary immunodeficiency diseases. *Clin Exp Immunol* 109 (Suppl. 1):1–28, 1997
3. Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C: NIH conference: new insights into common variable immunodeficiency. *Ann Intern Med* 118: 720–730, 1993
4. Young RJ, Duncan LJP, Paton L, Yap PL: Development of insulin-dependent diabetes in adult-onset hypogammaglobulinaemia. *Br Med J* 282:1668, 1981
5. Conley ME, Park CL, Douglas SD: Childhood common variable immunodeficiency with autoimmune disease. *J Pediatr* 108: 915–922, 1986
6. Moffitt JE, Guill MF, Leffell MS, Ades EW, Burek CL, Lobel SA, Hoffman WH: Type I diabetes in adolescent with common variable immunodeficiency. *J Allergy Clin Immunol* 84:191–196, 1989
7. Kuijpers TW, de Haas M, de Groot CJ, von dem Borne AK, Weening RS: The use of rh-GCSF in chronic autoimmune neutropenia: reversal of autoimmune phenomena, a case history. *Br J Haematol* 94:464–469, 1996

Utility of the American Diabetes Association Risk Test in a Community Screening Program

The current American Diabetes Association (ADA) risk test, "Take the test. Know the score," was used as a screening and educational tool in a community diabetes outreach program (1). Outreach workers went into underserved urban communities in Onondaga County, NY and presented over 40 educational programs on diabetes. As part of the program, participants were encouraged to take the ADA risk test and were offered a free plasma glucose test by venipuncture, especially if scoring ≥10 on the risk test.

Table 1—*Sensitivity and specificity of the ADA diabetes risk test in a community screening program*

Group	*n*	Sensitivity of risk test (%)	Specificity of risk test (%)	Prevalence of diabetes and IGT (%)	Positive predictive value
Total	396	80	34.6	8.8	11.9
African-American	148	90.9	24.8	7.4	9.7
Caucasian	198	72.7	40.9	11.1	13.3
Female	309	84.6	32.2	8.4	10.3
Male	85	66.7	43.4	10.6	12.2

Demographic information, risk test scores, and plasma glucose levels were recorded. Individuals with abnormal glucose levels received follow-up testing. Abnormal glucose levels were defined as a fasting glucose >109 mg/dl or a random glucose >159 mg/dl, levels that define impaired glucose tolerance (IGT) or diabetes. A positive ADA risk test was defined as a score of ≥10.

Of the >1,000 individuals who attended these programs, 396 people both completed the risk test and had their plasma glucose measured. The average age of the participants was 51.0 ± 15.0 years (SD). Although our data were not collected as part of a randomized trial, they provide information on the utility of the risk test in a community screening program (Table 1).

For the risk test to be of value, the sensitivity should be high, since the consequences of not diagnosing the disease are tremendous. Diabetes has preventable complications, and early treatment is necessary. Specificity is less important because the test to rule out diabetes is not burdensome—a fasting plasma glucose test is inexpensive, easy to perform, and minimally invasive.

Given that the test should have a high sensitivity, the ADA risk test performed less than ideally, particularly in Caucasians and males. The risk test is weighted against males because one of the questions is directed at women only. Of the false negatives, four had glucose levels >300 mg/dl. These individuals probably would have been detected based on the recommendation to screen people with symptoms of diabetes.

Our recommendation, given these results, is to de-emphasize the numeric risk score in the ADA's Community Campaign for Diabetes materials. People need to be made aware of risk factors associated with the development of diabetes and of the symptoms of diabetes. Risk factors not included in the ADA risk test, such as hypertension, high-risk ethnicity, history of gestational diabetes, past IGT, and dyslipidemia should also be emphasized (2). It is important to stress that one can have a low score and still have diabetes. The new screening recommendations (2), which advocate screening everyone >45 years every 3 years, beginning earlier and testing more frequently if risk factors are present, should be emphasized rather than a specific risk test score.

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References

1. Herman WH, Smith PJ, Thompson TJ, Englegau MM, Aubert RE: A new and simple questionnaire to identify people at increased risk for undiagnosed diabetes. *Diabetes Care* 18:382–387, 1995
2. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997

Response to Knudson et al.

We congratulate Knudson, Turner, Sedore, and Weinstock on their diabetes outreach activities in Onondaga County (1) and appreciate the opportunity to comment on their findings. Specifically, we appreciate the opportunity to comment on the performance of the diabetes screening questionnaire, "Take the test. Know the score," developed by Dr. Richard Kahn and the American Diabetes Association (ADA) based on our work.

In our work, classification trees were applied to data from the second National Health and Nutrition Examination Survey (NHANES) to identify subsets of people at increased risk for previously undiagnosed diabetes (2). Diabetes was defined by a fasting glucose ≥140 mg/dl or a glucose 2 h after a 75-g oral glucose level ≥200 mg/dl. We found that a classification tree incorporating age, sex, obesity, sedentary lifestyle, family history of diabetes, and history of the delivery of a macrosomic infant was 79% sensitive and 65% specific in identifying individuals with previously undiagnosed diabetes in a representative sample of the U.S. population. To develop the "Take the test. Know the score." questionnaire, the ADA applied arbitrary weights to risk factors to identify subjects in the terminal leaves of the classification tree who were at increased risk.

The performance of this classification tree was essentially identical to that of one that incorporated the same demographic and historical variables and also included history of glucose intolerance and history of hypertension (2). Its performance was, however, significantly better than that of a risk factor questionnaire previously used by the ADA (2). We estimated that use of the classification tree would result in follow-up testing to establish a definitive diagnosis of diabetes in 31% of the total U.S. population (2). The trade-off was that ~20% of individuals with undiagnosed diabetes would be missed with the initial screen (2). We concluded that the primary value of the screening questionnaire was to render a general population to a smaller group that would have a higher prevalence of diabetes, thus making the subsequent application of biochemical tests more efficient. This was particularly important when the definitive diagnostic test for diabetes was the oral glucose tolerance test,